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Theoretical Studies on the Bifunctionality of Chiral Thiourea-Based Organocatalysts: Competing Routes to C–C Bond Formation

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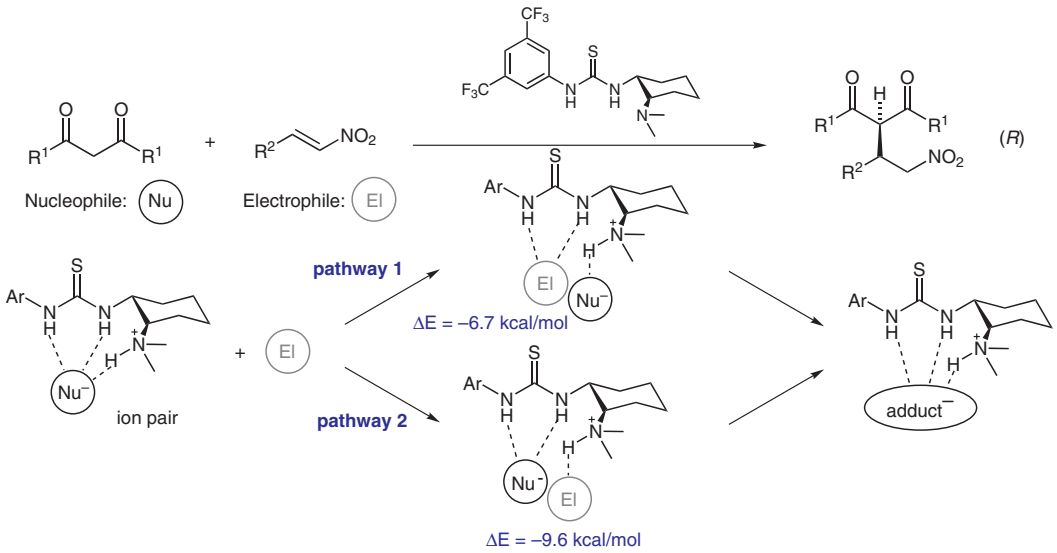
Theoretical Studies on the Bifunctionality of Thiourea-Based Organocatalysts



Significance: A computational mechanistic study of the enantioselective Michael addition of acetylacetone to nitroolefin promoted by a thiourea-based chiral bifunctional organocatalyst is presented. The optimal structural arrangement of the active sites of the catalyst has been attained via protonation of its basic center by the nucleophilic substrate through a reversible kinetic process. The generally accepted mechanism for the adduct formation involves electrophile activation through hydrogen bonds with the thiourea moiety and subsequent C–C bond formation between simultaneously activated components (pathway 1). An alternative reaction mechanism for the C–C coupling step is the electrophile activation by the protonated amine group of the catalyst (pathway 2), involving a ternary H-bonded complex and a transition state more stable than those formed along the former pathway. Both reaction pathways account for the observed enantioselectivity.

Comment: The enantioselective Michael addition of nucleophiles to nitroolefins represents one of the most extensively studied thiourea-organocatalyzed reactions. Recently, a novel bifunctional thiourea catalyst combining H-bond donors and a chiral tertiary amine group has been developed by Takemoto. It has been assumed that the two substrates involved in the reaction are activated simultaneously: the nitroolefin via multiple H-bonds with the thiourea moiety and the nucleophile through interactions with the tertiary amine group and subsequent deprotonation, followed by C–C bond creation via the formation of a ternary H-bonded complex (Y. Takemoto et al. *J. Am. Chem. Soc.* **2005**, *127*, 119-125). In this paper, theoretical investigations showed that the energetically more favorable pathway to form the Michael product takes place via nitroolefin activation by the protonated tertiary amine group. Further mechanistic studies are required to confirm and generalize the proposed mechanism.

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